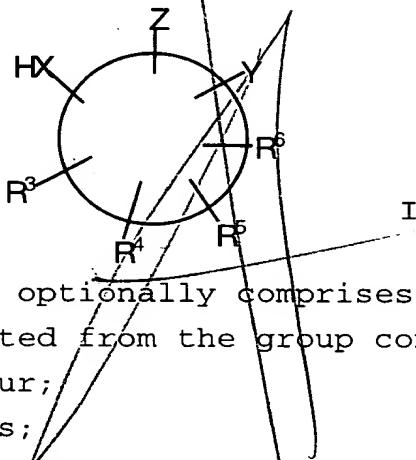


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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of  
5 a) synthesis of a linear or cyclic peptide,  
b) synthesis of a C-terminal modified peptide, or  
c) on-resin cyclisation of a peptide molecule,  
comprising the step of linking a cyclic aromatic or alkyl auxiliary compound of General Formula I to an amine nitrogen atom.

10



in which the ring optionally comprises one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur;  
is of 5 to 7 atoms;  
15 comprises 3 carbon atoms substituted respectively by XH, Z, and Y; and  
is additionally substituted by groups R<sup>3</sup> and R<sup>4</sup> when the compound is a 5-membered ring, or is additionally substituted by groups R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> when the compound is a 6-membered ring, or is additionally substituted by groups R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> when the compound is a 7-membered ring,  
20 in which  
X is oxygen, sulphur, CH<sub>2</sub>O-, or CH<sub>2</sub>S-;  
Y is an electron-withdrawing group;  
25 Z is any group which allows the formation of a covalent carbon-nitrogen bond; and  
R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted

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heteroaryl, alkoxy, aryloxy, XH or Y, or a covalent linkage to a solid support, and  
in which R<sup>3</sup> and R<sup>4</sup>, R<sup>4</sup> and R<sup>5</sup> or R<sup>5</sup> and R<sup>6</sup> can optionally together with the ring form a 5-, 6-, or 7-membered ring,  
5 thereby to facilitate conversion of the amine to an amide.

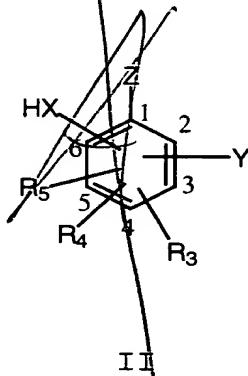
2. A method according to claim 1, in which Y is  
nitro, ketone, carboxylic ester, amide, nitrile,  
sulfonamide, sulfoxide, sulfone, sulfonate, fluoride,  
10 chloride, bromide or iodide.

3. A method according to claim 1 or claim 2, in  
which Z is an aldehyde, alkylalcohol, alkylhalide, or a  
ketone, or is a halogenated C<sub>1-3</sub>alkyl group.

15 4. A method according to claim 3, in which the  
halogenated alkyl group is a methyl group.

20 5. A method according to claim 3 or claim 4, in  
which the halogen is iodine, bromine or chlorine.

25 6. A method according to any one of Claims 1 to 5,  
in which the auxiliary compound is of general Formula II



30 7. A method according to any one of claims 1 to 6,  
in which the XH group is at position 2 or 3 in General  
Formula I or General Formula II, and Y is at any other  
position.

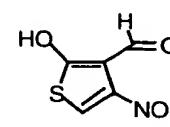
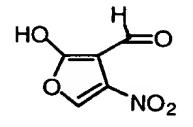
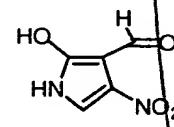
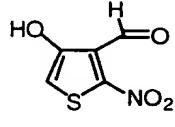
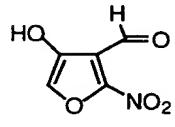
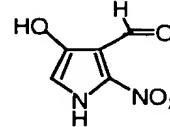
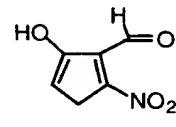
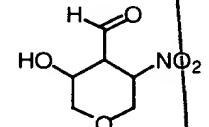
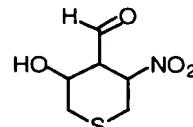
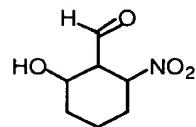
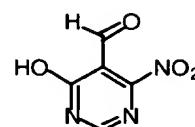
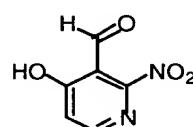
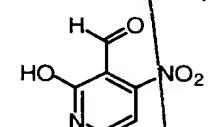
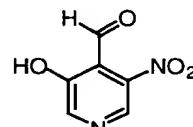
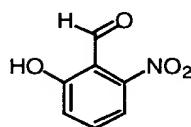
8. A method according to claim 7, in which the XH group is at position 2.

5 9. A method according to any one of claims 1 to 8, in which Y is at position 6.

10. 10. A method according to claim 9, in which Y is NO<sub>2</sub>.

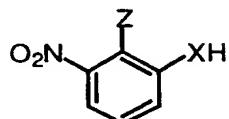
10 11. A method according to any one of claims 1 to 4, in which the auxiliary compound is selected from the group consisting of

15



12. A method according to claim 1 for synthesis of a cyclic peptide, a large peptide, or a difficult peptide, in which the auxiliary compound is of General Formula III

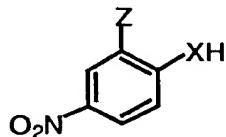
5



III

10 and the auxiliary compound is removed by photolysis following amide bond formation.

13. A method according to claim 1 for synthesis of a cyclic peptide, a large peptide, or a difficult peptide containing one or more substituted amide bonds, in which 15 the auxiliary compound is not removed, and the auxiliary compound is of General Formula IV



20

IV

14. A method of

25 a) synthesis of a compound selected from the group consisting of linear and cyclic peptides, large peptides with a native peptide backbone, and "difficult" peptide sequences,

30 b) backbone linkage for the synthesis of peptides, C-terminal modified peptides, or  
c) on-resin cyclisation,

comprising the step of linking a cyclic auxiliary compound of General Formula I, General Formula II, General Formula III, or General Formula IV to an amine nitrogen atom, thereby to facilitate conversion of the amine to an amide.

5 15. A method according to claim 14, in which XH in General Formula III is at position 2, and Y is NO<sub>2</sub> at position 6.

10 16. A method according to claim 1 or claim 15, in which R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, and a covalent linkage to a solid support.

15 17. A method of synthesis of a cyclic peptide, comprising the steps of  
20 a) synthesising a linear peptide to be cyclised,  
b) linking an auxiliary compound as defined in any one of claims 1 to 11 to a desired primary amine of the linear peptide,  
c) activating a desired carboxylic acid to effect cyclisation, and where necessary inducing ring contraction, and optionally  
25 d) removing the auxiliary compound after complete N-acylation.

30 18. A method according to claim 17, in which ring contraction is induced by heating or by addition of a metal.

35 19. A method according to claim 17 or claim 18, in which the auxiliary compound is of General Formula III, and the auxiliary compound is removed by photolysis.

20. A method according to any one of claims 17 to 19, in which steps a) to d) are performed on a solid support,

and are followed by cleavage of the cyclic product from the solid support, and if desired, removal of side chain protecting groups.

5 21. A method according to any one of claims 17 to 19, in which activation of the C-terminal carboxylic acid is performed in the presence of an auxiliary compound of General Formula III, and the cyclisation is performed by attaching the auxiliary compound to the desired amine via the Z-group.

10 22. A method of synthesis of a large peptide with a native peptide backbone, comprising the steps of

- 15 a) synthesising a set of peptide fragments to be linked to form a large peptide,
- b) linking an auxiliary compound as defined in any one of claims 1 to 11 to the primary amine of the first peptide fragment,
- c) activating the carboxylic acid of the second peptide fragment,
- d) adding the second peptide fragment to the first peptide fragment and forming a peptide bond between the two fragments, and optionally
- e) removing the auxiliary compound after N-acylation is complete.

25 23. A method according to claim 21, in which the auxiliary compound is of General Formula IV, and the auxiliary compound is removed by photolysis.

30 24. A method of synthesis of a difficult peptide sequence, comprising the steps of

- 35 a) linking an auxiliary compound as defined in any one of claims 1 to 10 to one or more nitrogen atoms in peptide bonds of a peptide linked to a solid support,
- b) synthesising the complete peptide using standard solid phase synthesis methods, and optionally

c) when synthesis is complete, removing the auxiliary compound.

25. A method according to claim 24, in which the auxiliary compound is of General Formula III, and the auxiliary compound is removed by photolysis.

26. A method of backbone linkage for synthesis of a linear peptide, comprising the steps of

10 a) using an auxiliary compound as defined in any one of claims 1 to 11 as a linker linking the  $\alpha$ -nitrogen of an acid residue in the desired peptide to a solid support,

15 b) assembling the linear peptide using standard solid phase peptide synthesis methods, and optionally

c) removing the side chain protecting group(s), and/or

d) cleaving the peptide from the solid support.

20 27. A method according to claim 26, in which the carboxylic acid group of the C-terminal amino acid residue is replaced by a functional group.

25 28. A method according to claim 26, in which the carboxylic acid group of the C-terminal amino acid residue is replaced by an ester, alkylalcohol, acetal or amide group.

30 29. A method according to any one of claims 26 to 28, in which Y is nitro in position 6, XH is in position 2, and cleavage is performed by photolysis.

35 30. A method of on-resin cyclisation of a linear peptide, comprising the steps of

a) using an auxiliary compound as defined in any one of claims 1 to 11 as a linker linking the  $\alpha$ -nitrogen of an amino acid residue in the desired peptide to

a solid support,

b) synthesising a linear peptide on a solid support, using standard solid phase peptide synthesis methods,

5 c) deprotecting the desired amine and carboxylic acid groups,

d) activating the carboxylic acid group to perform cyclisation, and optionally

e) deprotecting amino acid side chain groups,  
10 and/or  
f) cleaving the cyclic peptide from the solid support.

31. A method according to claim 30, in which Y is a  
15 nitro group in position 6, XH is in position 2, and  
cleavage is performed by photolysis.

32. An auxiliary compound according to any one of  
General Formulae I, II, III or IV as respectively defined  
20 in claims 1, 12 and 13, linked to a support suitable for  
solid phase peptide synthesis.

33. An auxiliary compound linked to a support, as  
defined in claim 32, in which the support is selected from  
25 the group consisting of functionalised polystyrene resins,  
tentagel resins, and polyethyleneglycol resins.

34. A kit for use in synthesis of a peptide, cyclic peptide, comprising:

30 a) an auxiliary compound as defined in any one of claims 1 to 11, or

b) an auxiliary compound as defined in any one of claims 1 to 11, linked to a solid support, together with one or more reagents for solid phase peptide synthesis.